Guillain-Barré Syndrome and Influenza Virus Infection

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Background. In Western countries, the cause of 60% of all Guillain-Barré syndrome (GBS) cases remains unidentified. The number of cases of unidentified cause peaks in winter, and these cases are commonly preceded by respiratory tract infection or influenza-like illness. We investigated the triggering role of influenza virus infection.

Methods. Of 405 patients with GBS who were admitted to a French reference center during 1996–2004, 234 had cases caused by an unidentified agent. We used time-series methods to study the correlation between the monthly incidence of such cases and influenza-like illnesses reported by the Sentinelles surveillance network. We analyzed anti-influenza antibodies using complement fixation testing and hemagglutination-inhibition assays. We studied etiological subgroups using Wilcoxon and Fisher's exact tests.

Results. We found a positive association between the monthly incidence of GBS caused by an unidentified agent and reported influenza-like illnesses. Of 73 patients whose cases occurred during periods in which there was a possible link to influenza, 10 (13.7%) had serological evidence of recent influenza A, and 4 (5.5%) had serological evidence of influenza B. Eight of 10 influenza A–related cases occurred during "major" influenza seasons, and antibodies specific to the current epidemic strain were found in 9 cases. Most patients with influenza A–related cases were aged <65 years, and none had antiganglioside antibodies. Influenza-related cases differed both from *Campylobacter jejuni*–related cases, with regard to the lack of need for mechanical ventilation ($P = .014$), and from the cases caused by an unidentified agent, with regard to the presence of preceding influenza-like illness or respiratory tract infection ($P = .015$) and longer time from the infectious event to GBS onset ($P = .04$).

Conclusions. Influenza viruses are infrequent triggering agents of GBS but may play a significant role during major influenza outbreaks. Influenza-related GBS displays specific features and is not associated with antiganglioside antibody response, which suggests the presence of underlying immune mechanisms.

Guillain-Barré syndrome (GBS) is the most common cause of acute flaccid paralysis in poliomyelitis-free regions [1]; the estimated incidence of GBS is 0.4–4.0 cases per 100,000 population per year [2]. Most cases are thought to result from an aberrant immune response triggered by a recent infectious disease or vaccination. GBS occurs after acute infectious disease (usually respiratory tract infection [RTI] or gastrointestinal illness [GI]) in 60%–70% of patients [3]. *Campylobacter jejuni* and cytomegalovirus are the most commonly identified infectious causes in Western countries, accounting for 13%–39% and 10%–15% of GBS cases, respectively [1, 4, 5]. Other possible infectious causes include Epstein-Barr virus, *Mycoplasma pneumoniae,* and *Haemophilus influenzae* [1, 4, 5]. Vaccinations have also been implicated in GBS; an example is the influenza vaccine used during the mass vaccination campaign

against swine influenza in the United States from 1976 through 1977 [6]. However, 60%–70% of GBS cases in Western countries remain without any identified cause.

We recently reported that, in the greater Paris area, GBS caused by an unidentified agent (i.e., not related to the aforementioned agents) occurred more frequently during the winter season and was commonly preceded by RTI or influenza-like syndrome (ILS) [5]. These results were recently supported by Tam et al. [7], who demonstrated a significant association between the weekly number of GBS-related hospitalizations in England and the weekly number of laboratory reports of influenza cases. However, the cases in those studies were not virologically documented, and no information was provided about either the characteristics of the cases that were possibly linked to influenza or the virus types involved.

Here, we demonstrate a direct link between GBS and recent influenza virus infection. However, we show that influenza-related cases are uncommon and, in France, are mainly observed during major outbreaks of influenza. We also show that influenza-related cases constitute a distinctive entity and that they are not associated with the generation of antiganglioside antibodies; these findings suggest that a specific pathological mechanism may be involved in influenza-related GBS.

PATIENTS AND METHODS

Background information. The medical intensive care unit at the Raymond Poincaré Hospital (Garches, France) is a regional reference center for the management of adult patients with GBS. All patients with GBS who are admitted to the hospital are asked to participate in current therapeutic protocols. Participating patients are observed prospectively for 12 months, as described elsewhere [5, 8–11]. Clinical data collection, serum antibody detection, and electrophysiological testing are part of current treatment of patients admitted to our health care center to treat GBS. Study of anti-influenza antibodies was performed using a declared serum collection, according to the French legislation. No further ethical approval was required for this study.

Study population. Four-hundred five patients with clinically defined GBS (according to the criteria of Asbury and Cornblath [12]), were admitted consecutively during 1996–2004. At hospital admission, pretreatment serum samples were obtained and clinical data were collected—namely on infectious events (GI, RTI, ILS, and other), vaccinations within the 2 previous months, and time from the onset of the infectious event to the onset of neurological signs [5, 11]. Serum antibody titers against *C. jejuni, M. pneumoniae,* cytomegalovirus, and Epstein-Barr virus were determined, as described elsewhere [5]. Antigangliosides IgM and IgG were detected by immunodot blot and enzymatic immunoassay (GanglioCombi; Bühlmann

Laboratories) [13]. Electrophysiological testing was performed using a Neuropack SIGMA EMG device (MESA Nihon Kohden), as described elsewhere [9].

Data from surveillance networks. We used data provided by 2 independent surveillance networks: Sentinelles and Groupes Régionaux d'Observation de la Grippe (Regional Influenza Surveillance Group). Sentinelles is a national network that collects clinical reports of illnesses, such as influenza-like illness (ILI; defined as sudden fever [temperature, >39°C], myalgia, and respiratory signs) and acute GI, from general practitioners. The number of cases is reported weekly at the Sentinelles Web site [14]. Groupes Régionaux d'Observation de la Grippe is an influenza-monitoring network; it collects clinical reports of acute RTI from general practitioners and pediatricians and virological data from the same community. Data on past and current epidemics are available at the Groupes Régionaux d'Observation de la Grippe Web site [15].

Time-series methods. The analysis of the relationship between the incidence of GBS caused by an unknown agent and the incidence of ILI or GI was performed using the time-series methods, after some seasonal adjustment to avoid the detection of spurious associations that reflect only a similar seasonality [16]. As described elsewhere [17], we tested the link between the patterns of GBS and ILI cases that were not explained by usual seasonal variation, which is more easily interpreted in terms of a possible direct influence of ILI on GBS. This interpretation can be strengthened by evidence of the unidirectionality of the association of one series toward the other, which is tested by lagged correlation or regression. First, the expected seasonal variations in the numbers of cases of GBS(t) (i.e., the number of cases of GBS caused by an unknown agent that were observed during month t) and ILI(t) (i.e., the number of cases of ILI during month t) were estimated using usual periodic modeling of time series. Because the number of cases of GBS was low, all data were analyzed on a monthly rather than weekly periodicity; a Poisson model was used for GBS(t), as proposed by Jones et al. [18]. This model supposes that GBS(t) is a Poisson variable of mean $\mu(t)$, with

$$\log \mu(t) = a_0 + a_1 t + a_c \cos\left(\frac{2\pi t}{12}\right) + a_s \sin\left(\frac{2\pi t}{12}\right).$$

Because we have already revealed a yearly seasonality with regard to the number of cases of GBS caused by unknown agents [5], no higher-order harmonics were added to this model. We subsequently defined the residual variation in the number of GBS cases by the difference between the numbers of observed and expected cases, as follows:

$$R_{gb}(t) = GBS(t) - \mu(t).$$

A similar methodology was used for ILI(t), but higher numbers of cases allowed a direct periodic model, as follows:

$$\mathrm{ILI}(t) = b_0 + b_1 t + b_c \cos\left(\frac{2\pi t}{12}\right) + b_s \sin\left(\frac{2\pi t}{12}\right) + R_f(t).$$

$R_f(t)$ is the residual variation in the number of ILI cases. After $R_{gb}(t)$ and $R_f(t)$ were obtained, cross-correlation plots of both series at different time lags were computed to detect association between both series. As proposed by Hubert et al. [17], lagged regression with autocorrelated errors was also used, with the model

$$R_{gb}(t) = \alpha + \beta R_f(t - k) + e(t).$$

The hypothesis tested is the existence of an association between residual variation in the number of GBS cases during month t and residual variation in the number of cases of ILI during month $(t - k)$. Lags k were between -6 and 6; negative lags allowed verification if the association was directional. To show a potential causal relationship between ILI and GBS, we would expect that some of the backward-lagged ($k > 0$) regression coefficients or cross-correlation coefficients would be statistically significant and that none of the forward-lagged ($k < 0$) coefficients would be statistically significant. Because of high serial correlation, the models for each value of k were fit separately, and an autoregressive structure for the residual errors $e(t)$ was allowed in the model. Similar methodology was used for analysis of GBS and GI cases.

Other statistical methods. Characteristics of patient subgroups were compared using the Fisher's exact test and the Wilcoxon rank-sum test. To account for multiplicity, P values were adjusted by Hochberg's method [19]. All tests were 2 tailed, and statistical significance was set at $P = .05$; analyses were performed using R software, version 2.4.0 (The R Foundation for Statistical Computing).

Influenza serology. Antibodies to influenza A and B were assayed by complement fixation tests (CFT; Virion/Serion), and recent infection was defined by titers ≥ 64. Anti–influenza A antibodies directed against vaccine and circulating strains were measured by hemagglutination-inhibition (HAI) assays, as described elsewhere [20]. Corresponding postinfectious ferret serum samples were tested as control samples. Serum samples were independently tested against 4 hemagglutinin units of each virus, and HAI assays were performed with 0.5% guinea pig erythrocytes. Nonspecific erythrocyte agglutination was ruled out by mock HAI.

RESULTS

The occurrence of cases of GBS caused by unidentified agents correlates with peaks in the incidence of ILI. Of the 405

patients, 171 patients (42%) had serological evidence of recent infection due to a known causative agent (103 patients had infection due to *C. jejuni*, 56 had infection due to cytomegalovirus, 10 had infection due to *M. pneumoniae*, and 4 had infection due to Epstein-Barr virus), and 234 patients (58%) had GBS caused by an unidentified agent (figure 1). The dates of GBS onset in the 234 patients with GBS caused by an unidentified agent were compared with the monthly incidence of both acute ILI and GI (provided by the Sentinelles network). Cross-correlation plots and lagged regression with auto-correlated errors—combining series of cases of ILI and cases of GBS caused by an unidentified agent—revealed a positive association between the 2 disorders, with a significantly elevated ILI incidence both 1 and 2 months before GBS onset ($P = .004$ and $P = .044$, respectively) (figure 2). No statistically significant associations were found for backward lag times (i.e., no correlation was found for GBS caused by an unidentified agent before the occurrence of ILI). This directionality of the association supports a causal link between GBS caused by an unidentified agent and ILI. The specificity of this link was also supported by the lack of any statistically significant association between GBS caused by an unidentified agent and reported cases of GI or between GBS caused by an identified agent and reported cases of ILI (data not shown).

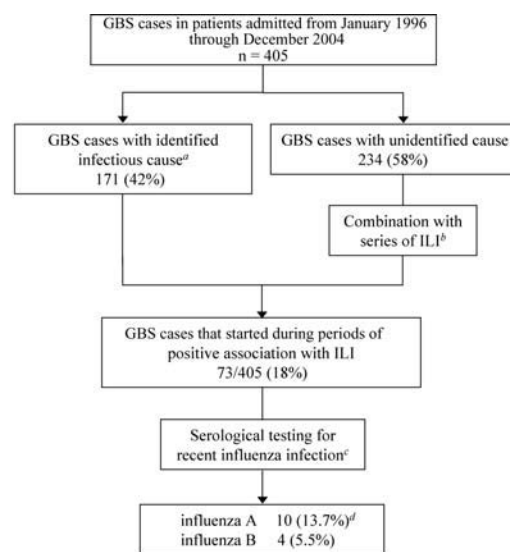***Influenza-related cases of GBS mainly occur during major influenza seasons and involve current epidemic strains.***

Figure 1. Flow of cases through the study. [a]One hundred three cases (60%) due to *Campylobacter jejuni*, 56 (32%) due to cytomegalovirus, 10 (6%) due to *Mycobacterium pneumoniae*, and 4 (2%) due to Epstein Barr virus. [b]By cross-correlation plots and lagged regression with autocorrelated errors. [c]By complement fixation testing. [d]Nine of 10 patients presented with significant hemagglutination-inhibition titers against the current epidemic strain. GBS, Guillain-Barré syndrome; ILI, influenza-like illness.
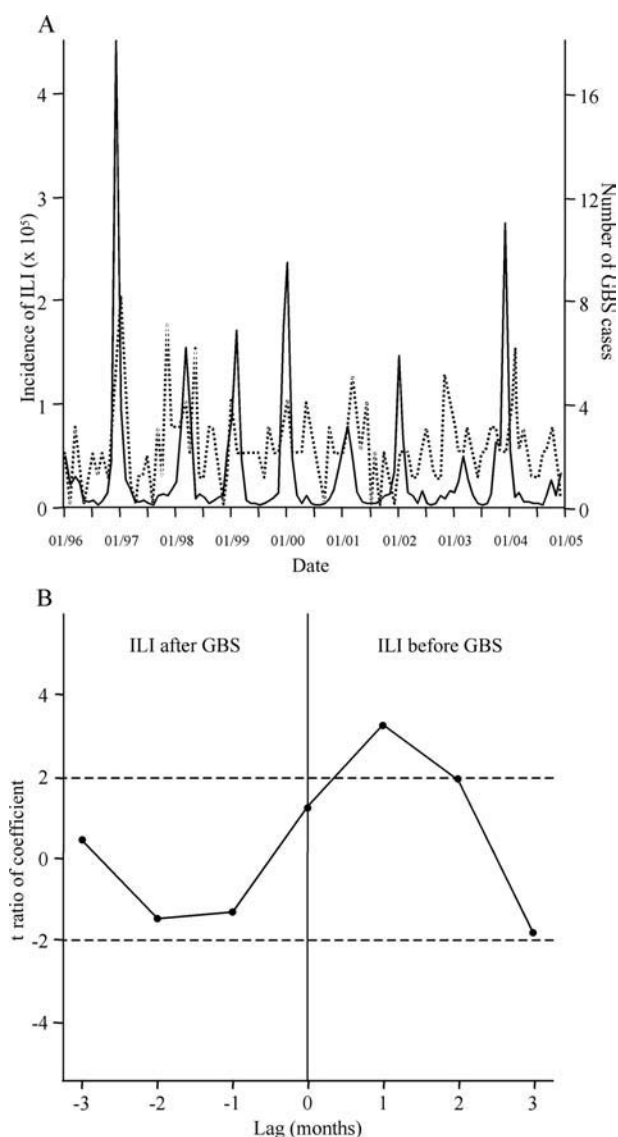
during 1996–2004) were used as control samples and were tested. CFT titers were <64 in all patients but 1 (median titer, 16). Other causative agents recognized by serological testing included *C. jejuni* (in samples from 14 patients; 19.2%), cytomegalovirus (5; 6.8%), and Epstein-Barr virus (1; 1.4%); 2 patients had serological evidence of recent infection due to both *C. jejuni* and influenza viruses (table 1) [21, 22].

The 10 cases of GBS in patients with serological evidence of recent influenza A were not evenly distributed from 1996 through 2004 (figure 3). Eight cases occurred during 2 seasons that were considered to be "major" in terms of influenza activity: 1996–1997 (4 cases) and 1999–2000 (4 cases) [23]. In addition, season 1996–1997 was characterized by the circulation of the A/Nanchang/933/95(H3N2) virus, which accounted for an unusually high morbidity rate. The 2 remaining cases occurred during "moderate" seasons (1997–1998 and 1998–1999), and no case was detected from 2000 through 2004, when influenza activity was "mild" [23].

For each influenza A–related case, we used HAI to study the specific reactivity of influenza A antibodies against each viral strain circulating from 1995 (1 year before the study period) through 2000 and against the corresponding vaccine strains (figure 4). All patients but 1 (no specific HAI activity against tested strains) presented with significant HAI titers against the epidemic strain from the season of their GBS onset. One patient, who had been vaccinated 15 days before the onset of neurological symptoms, presented with high titers of reactivity (>1280) against both vaccine and circulating strains. These results suggested that the patient might have developed influenza shortly after (and despite) vaccination and then developed influenza-related GBS.

Characteristics of GBS associated with recent influenza virus infection. The 14 patients with serological evidence of recent influenza virus infection comprised 8 male and 6 female patients (table 1). Nine of the 14 patients were aged <60 years, and 12 had ILS or RTI before GBS onset (time from ILS or RTI to GBS onset, 3–30 days). Only 1 patient had been vaccinated against influenza (15 days before GBS onset) (table 1). Thirteen patients presented with both sensory and motor defects. One patient developed bulbar dysfunction, and 5 developed facial palsy. Electrophysiological testing was performed for 9 patients, and testing revealed either demyelinating (4 patients) or equivocal (3 patients) profiles for most patients. None of the 14 patients had detectable antiganglioside antibodies. Seven patients were treated with plasma exchange, and the other 7 were treated with intravenous IgG. Only 2 patients, both with influenza B infection, received mechanical ventilation. One patient, with influenza A–related GBS, died, and 4 of 10 patients with available data had sequelae at a 1 year follow-up examination.

Influenza A–related GBS cases were compared with *C. jejuni*–

Figure 2. *A,* Monthly incidence of influenza-like illness (ILI; *solid line*) and Guillain-Barré syndrome (GBS; *dashed line*) caused by an unidentified agent. *B,* t Ratios of lagged-regression coefficients between residual cases of GBS caused by an unidentified agent at month t and ILI at month t − lag, for lags of −3 to 3. Horizontal dashed lines indicate 5% significance level of a 2-sided test of association.

Among the study population, 73 patients were selected because their neurological defects had started during periods of positive association with epidemic ILI (during the 2 months after and the 2 weeks before peaks in the number of cases of ILI, to reduce the risk of omitting cases) (figure 1). Of these 73 patients, 10 (13.7%) had serological evidence of recent influenza A virus infection (with CFT titers of 128–256), and 4 (5.5%) had serological evidence of recent influenza B virus infection (with CFT titers of 64–128). Sixty-six serum samples from patients with GBS caused by an unidentified agent that were obtained outside influenza seasons (from June through October

Table 1. Characteristics of patients with Guillain-Barré syndrome (GBS) associated with recent influenza virus infection.

Patient	CFT titer	Sex	Age, years	Date of GBS onset	Preceding event	Time from preceding event to onset of neurological defects, days	Neurological defects	Disability grade at nadir[a]	Use of mechanical ventilation	Electrophysiology[b] (time from onset of neurological defects to testing, days)	Treatment	Long-term outcome
With influenza A before GBS												
1	128	M	71	January 1997	LRTI	15	SM and BD	4	No	ND	PE	No sequelae
2	256	M	52	January 1997	ILS	30	SM and FP	4	No	ND	IVIg	NA
3[c]	128	M	50	January 1997	ILS	7	SM and FP	≤3	No	Normal (9)	IVIg	No sequelae
4	128	M	20	December 1996	ILS	7	SM	≤3	No	ND	PE	No sequelae
5	128	F	52	April 1998	ILS and GI	14	SM and FP	4	No	ND	IVIg	No sequelae
6	256	F	84	March 1999	GI	15	SM	4	No	Demyelinating (9)	PE	Death
7	128	F	50	January 2000	ILS and GI	5	SM	4	No	Equivocal (12)	IVIg	Sensory defects
8[d]	128	M	64	January 2000	LRTI	21	PM	4	No	Demyelinating (8)	PE	No sequelae
9	128	F	80	January 2000	LRTI	21	SM	4	No	Equivocal (9)	PE	NA
10	256	F	57	February 2000	URTI	25	SM and FP	≤3	No	Equivocal (9)	PE	Sensory defects
With influenza B before GBS												
1	64	M	49	April 1998	ILS and GI	7	SM and FP	4	No	ND	PE	Sensory defects
2	128	M	50	March 1999	LRTI	4	SM	5	Yes	Demyelinating (5)	IVIg	Motor defects
3	128	M	39	March 2001	URTI and GI	10	SM	5	Yes	Demyelinating (9)	IVIg	No sequelae
4[d]	128	F	74	February 2002	GI	3	SM	4	No	ND	IVIg	NA

NOTE. BD, bulbar dysfunction; CFT, complement fixation test; FP, facial palsy; GI, gastrointestinal illness; ILS, influenza-like syndrome; IVIg, intravenous immunoglobulin; LRTI, lower respiratory tract infection; NA, not available; ND, not done; PE, plasma exchange; PM, pure motor; SM, mixed sensitive and motor defects; URTI, upper respiratory tract infection.

a According to the Plasma Exchange/Sandoglobulin GBS Trial Group [21].
b According to Hadden et al. [22].
c Received influenza vaccine unusually late in the season (early January 1997) and presented with ILS 7 days after vaccination and GBS 15 days after vaccination.
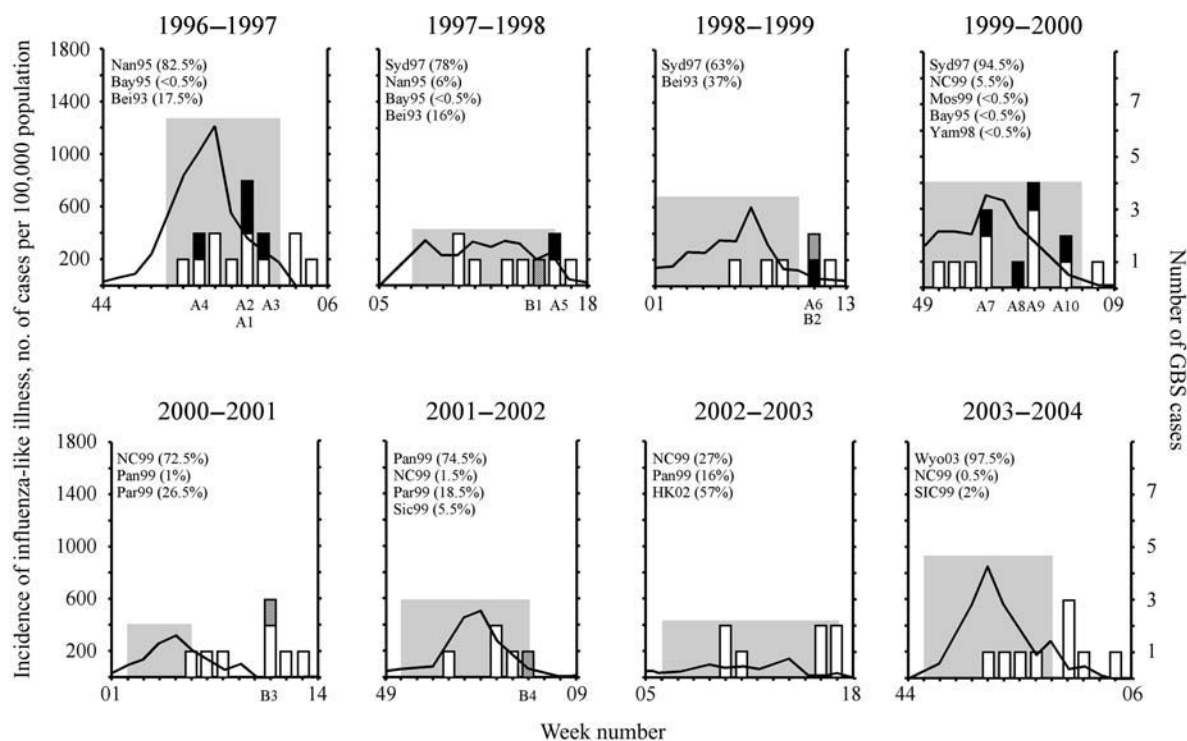d Presented with serological evidence of recent *Campylobacter jejuni* infection.

Figure 3. Distribution of the 73 Guillain-Barré syndrome (GBS) cases that occurred during epidemic seasons 1996–2004 by incidence of influenza-like illness and involved influenza strains in the greater Paris area. Weekly incidence of influenza-like illness, as provided by the Sentinelles surveillance network, is represented by black lines. Gray areas indicate periods of influenza virus circulation at epidemic rates, as provided by the National Influenza Centre (northern France). The circulating strains and their respective prevalence are indicated for each season. Boxes indicate the number of GBS cases during each studied season. Black boxes indicate cases related to influenza A, dashed boxes indicate cases related to influenza B, and white boxes indicate cases unrelated to influenza. Bay95, A/Bayern/7/95(H1N1); Bei93, B/Beijing/184/93; HK02, B/HongKong/1343/02; Nan95, A/Nanshang/933/95(H3N2); NC99, A/NewCaledonia/20/99(H1N1); Mos99, A/Moscow/10/99(H3N2); Pan99, A/Panama/2007/99(H3N2); Par99, B/Paris/1264/99 (antigenically related to BEI93); Sic99, B/Sichuan/379/99; Syd97, A/Sydney/5/97(H3N2); Wyo03, A/Wyoming/3/03(H3N2); Yam98, B/Yamanashi/166/98.

related cases and with GBS cases due to an unidentified agent for which influenza CFT results were negative (table 2). Because of the small number of cases, the influenza B subgroup was not included in the analysis. Patients with influenza A–related GBS were less likely to receive mechanical ventilation than were patients with *C. jejuni*–related GBS (0 of 9 patients vs. 7 of 12 patients; $P = .014$). Furthermore, patients with influenza A–related GBS were more likely to have preceding ILS and/or RTI (8 of 9 vs. 15 of 41; $P = .015$) and had a significantly longer duration between the infectious event and GBS onset (median, 15 days vs. 6.5 days; $P = .040$), compared with patients with GBS due to an unidentified agent who had negative influenza CFT results.

DISCUSSION

To our knowledge, this study is the first to provide evidence that influenza viruses are triggering agents of GBS. This was determined in 2 stages. First, we established a statistical link between cases of GBS unrelated to usual etiologies (i.e., *C. jejuni*, cytomegalovirus, Epstein-Barr virus, and *M. pneumon-*

iae) and cases of ILI in the French population; the incidence of ILI was notably high during the month before the peak number of admissions to our health care center for GBS caused by an unidentified agent. Second, we sought virological evidence of recent infection due to influenza A or B viruses in patients with GBS that had occurred within periods of positive association with epidemic ILI. Indeed, although ILI may be caused by numerous infectious agents, epidemics of influenza represent the most common etiology. Although it is time consuming, CFT was chosen to screen patients' samples for recent influenza. Indeed, CFT preferentially detects IgM and provides a particularly reliable means to detect recent viral infection [24–27]. This screening approach was then confirmed by strain-specific HIAs for cases related to influenza A virus.

The role of influenza viruses as triggering agents of GBS in our study is consistent with that in a recent nested case-control study, based on data from the United Kingdom General Practice Research Database during 1991–2001, which found a positive association between GBS and a number of infectious events (including *Campylobacter* infection, Epstein-Barr virus infec-

	Viral Strain								
Serum sample	H3N2 JHB94	H1N1 SIN86	H3N2 NAN95	H1N1 BAY95	H3N2 SYD97	H1N1 BEI95	H1N1 NC99	H3N2 MOS99	Mock
1996-1997									
A1	40	20	**80**	20	<20	<20	<20	<20	<20
A2	20	<20	**160**	<20	20	<20	<20	40	<20
A3	640	>1280	640	>1280*	40	320*	<20	20	<20
A4	160	<20	**640**	<20	20	40	40	<20	<20
1997-1998									
A5	<20	20	20	20	<20	<20	<20	<20	<20
1998-1999									
A6	320	<20	640	<20	**640***	20	20	**640***	<20
1999-2000									
A7	20	<20	80	<20	**640***	<20	<20	**640***	<20
A8	40	20	80	40	**640***	<20	20	**1280***	<20
A9	40	40	320	40	**1280***	40	20	**>1280***	<20
A10	<20	20	<20	<20	**80**	<20	**160**	160	<20
Ferret	640	160	>1280	>1280	>1280	640	320	>1280	<20

Figure 4. Hemagglutination-inhibition (HAI) reactivity against epidemic and influenza A vaccine strains for each influenza A–related case. Serum samples were tested against each prevalent strain from the period 1995–2004, as well as against vaccine strains when they were different from the epidemic strain. Reference serum samples from ferrets infected by each tested strain were included as control samples. Nonspecific erythrocyte agglutination was ruled out by mock infection. Strain A/Johanesburg/33/94(H3N2) (JHB94) was prevalent in 1995, one year before the study period; A/Singapore/6/86(H1N1) (SIN86) was included in the 1996–1997 and 1998–1999 vaccines, and A/Beijing/262/95(H1N1) (BEI95) was included in the 1999–2000 vaccines. Gray areas delimit relevant epidemic or vaccine strains for each considered season. Except for patient A5, high HAI titers were observed against the most prevalent strain for each season (boldface type). Note that this also applies to patient A3, who received influenza vaccine 15 days before developing neurological signs. Patient A6 presented with a serological profile suggestive of recent infection due to A/Sydney/5/97(H3N2) (SYD97) and with reactivity to JHB94 and A/Nanshang/933/95(H3N2) (NAN95), probably reflective of past infection or vaccination. Patient A10's profile suggests either a mixed infection due to A/NewCaledonia/20/99(H1N1) (NC99) and SYD97 (or A/Moscow/10/99(H3N2) [MOS99]) or a single current infection due to NC99; antibodies to SYD97 and MOS99 (H3N2 strains) reflected past infection or vaccination. *Cross-reactivity between strains A/Bayern/7/95(H1N1) (BAY95) and BEI95. **Cross-reactivity between strains SYD97 and MOS99, as evidenced after testing of serum samples from infected ferrets (results not shown).

tion, and ILI) during the 2 months preceding GBS onset [28]. This is also consistent with some anecdotal cases of GBS or GBS-related diseases that occurred after influenza, although these cases were mainly reported in pediatric patients [29, 30]. However, our data reveal that cases of influenza-related GBS occur relatively infrequently, and this may explain why no previous study has yet proved a direct link between influenza and GBS. In our study, of 405 patients with GBS who were hospitalized from 1996 through 2004, only 14 (3.5%) had evidence of recent influenza. Moreover, most cases were grouped within seasons of high influenza activity. Eight of 10 influenza A–related cases were detected during only 2 of the 8 influenza seasons covered by the study.

With consideration that the number of cases of clinical influenza per year in the greater Paris area was ∼300,000 during seasons 1996–1997 and 1999–2000 and that our health care center handles 20%–30% of GBS cases per year in the same area [5], it can be estimated that the incidence of influenza-related GBS relative to the number of cases of influenza is 4–7 cases of GBS per 100,000 cases of influenza. In comparison, the risk of developing GBS after *C. jejuni* infection has been estimated to be 1 case of GBS per 1000 cases of *C. jejuni* infection [31], which suggests that influenza viruses may either be poorly powerful GBS triggers or require specific host-susceptibility to trigger GBS.

Cases of GBS associated with influenza—more specifically, those involving influenza A viruses—appear to constitute a specific entity. Indeed, influenza A–related cases differed from other cases in our study: they involved a longer duration from the infectious event (most frequently ILS or RTI) to GBS onset (median, 15 days) and an absence of antiganglioside antibody response. None of these patients required mechanical ventilation, most had demyelinating or equivocal electrophysiological profiles, and none had an axonal profile. Our results are consistent with previous studies that revealed a longer time before GBS onset when it was preceded by acute respiratory infection than when it was preceded by GI and a less frequent requirement for mechanical ventilation in cases unrelated to *C. jejuni,* cytomegalovirus, Epstein-Barr virus, or *M. pneumoniae* [31, 32]. This suggests that there are specific immunopathological events leading from influenza A to GBS, possibly involving an autoimmune response to viral peptides, as has been suggested for cytomegalovirus [4].

Whether certain viral strains or subtypes have a greater ability than others to induce GBS remains an unanswered question. Most influenza A–related cases identified in our study involved H3N2 viruses, which were the prevalent subtypes involved in the 2 major influenza seasons of the study period (A/Nanchang/933/95 during 1996–1997 and A/Sydney/5/97 during 1999–2000). Thus, most influenza virus infections were caused by H3N2 viruses; this may explain the proportionally high number of GBS cases related to H3N2 virus in our study. The proportion of cases found to be related to influenza A virus (10 cases) or to influenza B virus (4 cases), consistent with the respective

Table 2. Analysis of influenza A–related Guillain-Barré syndrome (GBS), compared with GBS caused by *Campylobacter jejuni* and with GBS caused by an unidentified agent.

Characteristic	Patients with GBS, agent associated with GBS				
	Influenza A (n = 9)[a]	*C. jejuni* (n = 12)[b]	P[d]	Unidentified (n = 41)[c]	P[e]
M:F (95% CI)	0.8 (0.2–3.7)	2 (0.5–9.1)	.48	1.4 (0.7–2.8)	.48
Age, median years (range)	52 (20–84)	65 (26–91)	.48	60 (23–93)	.89
Infectious event			.23		.086
None	0 (0)	3 (25)		16 (39)	
≥1	9 (100)	9 (75)		24 (59)	
Gastrointestinal illness	3 (33)	2 (17)	.61	7 (17)	.61
Respiratory tract infection	3 (33)	2 (17)	.61	8 (20)	.61
Influenza-like syndrome	5 (56)	3 (25)	.20	7 (17)	.054
Respiratory tract infection and/or influenza-like illness	8 (89)	5 (42)	.067	15 (37)	.015
Other	1[f] (11)	3 (25)	.6	3 (7)	.6
Time from infectious event to neurological signs, median days (IQR)	15 (7–21)	10 (5–12)	.13	6.5 (4–8)	.040
Neurological sign					
Only motor symptoms	1 (11)	4 (33)	.43	11 (27)	.43
Facial palsy	4 (44)	4 (33)	.70	14 (34)	.70
Bulbar dysfunction	1 (11)	4 (33)	.67	9 (22)	.67
Disability grade ≤3	3 (33)	2[g] (17)	>.99	13 (32)	>.99
Mechanical ventilation	0 (0)	7 (58)	.014	10 (24)	.17
Antibodies to gangliosides	0/9 (0)	4/8[h] (50)	.058	3/28[i] (11)	.56
Death	1 (11)	1 (8)	>.99	4 (10)	>.99

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range.

[a] One patient was positive for both *C. jejuni* and influenza A virus and, thus, was excluded.
[b] Two patients were positive for both *C. jejuni* and influenza A and B viruses and, thus, were excluded.
[c] Patients who had GBS caused by an unidentified agent (with negative complement fixation test results).
[d] GBS associated with influenza A versus GBS caused by *C. jejuni*.
[e] GBS associated with influenza A versus GBS caused by an unidentified agent (with negative influenza complement fixation results).
[f] Influenza vaccination.
[g] Including the only case of Miller-Fisher syndrome identified among the 73 studied cases.
[h] Two patients had antibodies to GM1 IgG or IgG/IgM, and 2 patients had antibodies to GQ1b IgG.
[i] Two patients had antibodies to GM1 IgG or IgG/IgM, and 1 patient had antibodies to GD1a IgG.

prevalence of the 2 viruses in the studied influenza seasons, also argues for similar propensities of different influenza viruses to induce GBS. However, this does not preclude strain-specific traits possibly implicated in the genesis of GBS. Recent studies seem to indicate that the immune response triggered by influenza A virus is strain dependent [33].

The link between GBS and influenza has long been viewed as a link between GBS and influenza vaccination on the basis of the report of an abnormally high number of GBS cases during the mass vaccination campaign against swine influenza in the United States during 1976–1977 [6]. Our study demonstrates that there is also a risk of GBS after influenza virus infection in adults, with an expected frequency much higher than that after influenza vaccination using either inactivated vaccines (1 GBS case per 1,000,000 vaccinated persons [34–36]) or live attenuated vaccines (2 GBS cases per 2,500,000 vaccinated persons [37]). Tam et al. [28] recently provided evidence that influenza vaccination might actually protect against GBS. These authors pointed out that this finding was not inconsistent with an absolute increase in GBS risk after vaccination but that it indicated a smaller risk than that after

influenza. Influenza vaccination is highly recommended and freely administered in France to individuals aged >65 years. In our study, most of the patients with influenza-related GBS were aged <65 years, and this might be related to a protective effect of influenza vaccination. In addition to allowing avoidance of severe complications associated with influenza, influenza vaccination may thus protect against GBS and its long-term sequelae.

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